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| **Vasopressors during adult cardiac arrest – Epinephrine vs. no epinephrine**  |
| **Population:** | Adult individuals with cardiac arrest in any setting (our-of-hospital or in-hospital). |
| **Intervention:** | Vasopressor or a combination of vasopressors provided intravenously or intraosseously during cardiopulmonary resuscitation. |
| **Comparison:** | No vasopressor, a different vasopressor, a different combination of vasopressors, a different vasopressor dose, or a different timing of vasopressors provided intravenously or intraosseously during cardiopulmonary resuscitation. |
| **Main outcomes:** | Clinical outcome including survival, favorable neurological outcome, and health-related quality of life at hospital discharge, 30 days, 90 days, 180 days, and 1 year. |

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| ProblemIs the problem a priority? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | Cardiac arrest, both in the out-of-hospital and in-hospital setting, is relatively common and carries a very high morbidity and mortality. |  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial○ Small● Moderate (survival)○ Large○ Varies○ Don't know | For epinephrine compared with placebo, improvements in return of spontaneous circulation and survival at hospital admission are substantial. The improvement in survival (hospital discharge, 30-days, 3 months, 6 months, and 12 months) is moderate. Whether there is improvement in survival with favorable neurological outcome remains uncertain. The desirable effects appear more pronounced in non-shockable compared with shockable rhythms.

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| **Epinephrine compared to placebo – Any rhythm (Jacobs 2011, Perkins 2018)** |
| **Outcome** | **RR (95% CI)** | **RD (95% CI)** |
| Return of spontaneous circulation | 3.09 (2.82 to 3.39) | 243 more per 1000(from 211 more to 277 more) |
| Survival at hospital discharge | 1.44(1.11 to 1.86) | 10 more per 1000(from 2 more to 19 more) |
| Favorable neurological outcome at hospital discharge | 1.21(0.90 to 1.62) | 4 more per 1,000(from 2 fewer to 12 more) |
| **Epinephrine compared to placebo – Shockable rhythms (Jacobs 2011, Perkins 2018)** |
| **Outcome** | **RR (95% CI)** | **RD (95% CI)** |
| Return of spontaneous circulation | 1.68(1.48 to 1.92) | 185 more per 1,000(from 130 more to 250 more) |
| Survival at hospital discharge | 1.23(0.94 to 1.62) | 22 more per 1,000(from 6 fewer to 60 more) |
| Favorable neurological outcome at hospital discharge | 1.05(0.76 to 1.45) | 4 more per 1,000(from 21 fewer to 39 more) |
| **Epinephrine compared to placebo – Non-shockable rhythms (Jacobs 2011, Perkins 2018)** |
| **Outcome** | **RR (95% CI)** | **RD (95% CI)** |
| Return of spontaneous circulation | 4.45(3.91 to 5.08) | 254 more per 1,000(from 214 more to 301 more) |
| Survival at hospital discharge | 2.56(1.37 to 4.80) | 7 more per 1,000(from 2 more to 16 more) |
| Favorable neurological outcome at hospital discharge | 1.80(0.80 to 4.07) | 2 more per 1,000(from 1 fewer to 9 more) |

 | Additional considerations that were raised included the impact of increased return of spontaneous circulation on organ donation. |
| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial● Small○ Moderate○ Large○ Varies○ Don't know | There is no evidence in clinical trials that epinephrine specifically contributes to cerebral injury beyond its effect of increasing overall survival, including in patients who may have sustained neurological damage.

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| **Epinephrine compared to placebo – Any rhythm (Jacobs 2011, Perkins 2018)** |
| **Outcome** | **RR (95% CI)** | **RD (95% CI)** |
| Favorable neurological outcomeat hospital discharge | 1.21(0.90 to 1.62) | 4 more per 1,000(from 2 fewer to 12 more) |
| Favorable neurologic outcomeat 3 months \* | 1.30(0.94-1.80) | 5 more per 1,000(from 1 fewer to 13 more) |
| Favorable neurologic outcomeat 6 months \* | 1.34(0.96 to 1.88) | 5 more per 1,000(from 1 fewer to 13 more) |

\* Perkins 2018 only | Epinephrine likely increases the number of survivors with both favorable and unfavorable neurological outcomes, as observed in the PARAMEDIC2 trial.1,2 This apparent increase in survivors with unfavorable neurological outcome should not be interpreted as epinephrine directly causing unfavorable neurological outcomes, but rather reflects its efficacy in restoring circulation in patients who may already have sustained significant cerebral injury due to prolonged cardiac arrest. |
| Certainty of evidenceWhat is the overall certainty of the evidence of effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low○ Low● Moderate (survival)○ High○ No included studies | The certainty of evidence varies by outcome. There is high certainty of evidence for return of spontaneous circulation and survival at hospital admission; moderate certainty of evidence for survival at hospital discharge, 3 months, and 6 months; and low to moderate certainty of evidence for favorable neurological outcome at hospital discharge, 3 months, and 6 months.

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| **Comparison (OHCA)** | **Outcome** |
| **Return of spontaneous circulation** | **Survival at hospital discharge** | **Favorable neurological outcome at hospital discharge** |
| Epinephrine compared to placebo – Any rhythm | ⨁⨁⨁⨁High | ⨁⨁⨁◯Moderate | ⨁⨁⨁◯Moderate |
| Epinephrine compared to placebo – Shockable rhythms | ⨁⨁⨁◯Moderate | ⨁⨁⨁◯Moderate | ⨁⨁◯◯Low |
| Epinephrine compared to placebo – Non-shockable rhythms | ⨁⨁⨁⨁High | ⨁⨁⨁◯Moderate | ⨁⨁◯◯Low |

 | The variation in the certainty of evidence by outcome was largely due to the event rate for each outcome. There was higher statistical power to evaluate differences in return of spontaneous circulation (a more common event) than survival with favorable neurological outcome (a much less common event). The certainty of evidence for favorable neurological outcome at 3 months and 6 months was also lessened by a loss to follow-up. |
| ValuesIs there important uncertainty about or variability in how much people value the main outcomes? |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability● Possibly important uncertainty or variability○ Probably no important uncertainty or variability○ No important uncertainty or variability | A study suggests that patients value survival with favorable neurological outcome most highly.3 | The importance of neurological intact survival is generally agreed upon with recognition that survival without neurological recovery is an undesirable outcome for most patients. |
| Balance of effectsDoes the balance between desirable and undesirable effects favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison● Probably favors the intervention○ Favors the intervention○ Varies○ Don't know | See above summary of desirable and undesirable effects. | Although there was no statistically significant effect from epinephrine on survival with favorable neurological outcome, the significantly difference in return of spontaneous circulation and survival led to the conclusion that the balance of effects favors the intervention. |
| Resources required |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs○ Moderate costs● Negligible costs and savings○ Moderate savings○ Large savings○ Varies○ Don't know |  | Resources might need to be allocated to communities that do not currently have capacity for administration of epinephrine in the out-of-hospital setting. |
| Certainty of evidence of required resourcesWhat is the certainty of the evidence of resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low○ Low○ Moderate○ High● No included studies |  |  |
| Cost effectivenessDoes the cost-effectiveness of the intervention favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison○ Probably favors the intervention○ Favors the intervention● Varies○ No included studies | Epinephrine use was associated with increased donation rates in a recent cost-effectiveness analysis of the PARAMEDIC2 trial (99 recipients from 40 donors in the epinephrine group vs 67 recipients from 24 donors in the placebo group) (Achana 2020 579). The analysis, incorporating both direct economic effects of survivors and indirect economic benefits of organ donation, yielded an incremental cost-effectiveness ratio for epinephrine of GBP 16,086 per quality-adjusted life year gained. | Costs are likely to be healthcare system specific. |
| EquityWhat would be the impact on health equity? |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced○ Probably reduced● Probably no impact○ Probably increased○ Increased○ Varies○ Don't know |  |  |
| AcceptabilityIs the intervention acceptable to key stakeholders? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no● Probably yes○ Yes○ Varies○ Don't know | We have not identified any research that assessed acceptability. However, the provision of epinephrine is currently the standard of care and would appear to be acceptable.  | Currently the standard of care is to provide epinephrine during cardiac arrest. Differential recommendations based on rhythm are also somewhat incorporated into current practice with recommendations to provide defibrillation prior to epinephrine for patients with shockable rhythms. |
| FeasibilityIs the intervention feasible to implement? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | Currently the standard of care is to provide epinephrine during cardiac arrest. |  |

|  | **Judgement** |
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| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | Small | **Moderate** | Large |  | Varies | Don't know |
| **Undesirable Effects** | Trivial | **Small** | Moderate | Large |  | Varies | Don't know |
| **Certainty of evidence** | Very low | Low | **Moderate** | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | **Possibly important uncertainty or variability** | Probably no important uncertainty or variability | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | **Negligible costs and savings** | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | **Varies** | No included studies |
| **Equity** | Reduced | Probably reduced | **Probably no impact** | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

# Conclusions

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| Recommendation |
| We recommend administration of epinephrine during cardiopulmonary resuscitation (strong recommendation, low certainty of evidence). For non-shockable rhythms (PEA/asystole), we recommend administration of epinephrine as soon as feasible during cardiopulmonary resuscitation (strong recommendation, very low certainty of evidence).For shockable rhythms (VF or pulseless VT), we suggest administration of epinephrine after initial defibrillation attempts are unsuccessful during cardiopulmonary resuscitation (weak recommendation, very low certainty of evidence).We suggest against the routine use of high-dose epinephrine in cardiac arrest (weak recommendation, very low certainty of evidence). |
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| Justification |
| In making the recommendation for epinephrine during cardiopulmonary resuscitation, we considered the findings that epinephrine substantially improves both return of spontaneous circulation, mid-term survival, and long-term survival as compared to placebo. There appears to be a more pronounced effect of epinephrine on return of spontaneous circulation and survival to hospital discharge in non-shockable rhythms compared to shockable rhythms, but assessment of these sub-groups should be taken with caution. For non-shockable rhythms, we recommend administering epinephrine as soon as feasible, given limited alternative interventions in most cases and chances of survival decreasing rapidly over time. Exceptions may exist where a clear reversible cause can be rapidly addressed. For shockable rhythms, the studies evaluating administration of epinephrine included protocols for provision after the third defibrillation. While the optimal timing in relation to defibrillations remains unknown, we suggest administering epinephrine after initial defibrillation attempts have been unsuccessful. |

# References

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